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Standardization of immunotherapy adverse events in patient information leaflets and development of an interface terminology for outpatients' monitoring

E.M. Zini[a,*], G. Lanzola[a], S. Quaglini[a], R. Cornet[b]

[a] Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Italy
[b] Department of Medical Informatics, Amsterdam Public Health Research Institute, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

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ABSTRACT

Introduction: Immunotherapy is effective for treating cancer, but it is also associated with a wide spectrum of adverse events. In order to detect them early, the patients need to be monitored at home, between the therapy administrations, e.g., by asking them to report outcomes, usually including symptoms and quality of life measures. For the collected data to be reusable, the symptoms need to be in a standardized form. The aim of this study is to explore the standardization of the information contained in the patient information leaflets (PILs) of immunotherapy drugs, by creating an interface terminology of immunotherapy-related adverse events, which should support a consistent collection of symptoms from the patients.

Methods: PILs contain a significant amount of information in free text, but they mix patient-reportable and clinically assessable events. We extracted a list of patient-reportable adverse events, mapped them to reference terminologies and compared the mapping results to choose the best-performing reference terminology.

Results: The PILs standardization led to the extraction of 151 symptoms and 424 terms, including both preferred terms and synonyms in English and Italian. Among the reference terminologies we considered, SNOMED CT allowed us to map all concepts and became, hence, the main reference terminology for the resulting interface terminology. A preliminary validation on the PIL of a new immunotherapy drug showed that our interface terminology already contained all the mentioned symptoms.

Conclusion: PILs provide a valuable source for determining adverse events. The resulting interface terminology includes Italian and English terms for patient-reportable adverse events for five immunotherapy drugs representative of their category. Further work will be undertaken to evaluate the usability of the interface terminology and the patients' experience and satisfaction with the proposed terms, made available for example through an app, as well as its effectiveness on data quality and quality of care.

1. Introduction

In the past few years, several new methods of treating cancer have emerged. Among these, immunotherapies are in rapid advancement. They increase the strength of the immune response against tumors, either stimulating the activities of specific components of the immune system or counteracting signals produced by cancer cells that suppress immune responses [1].

Immunotherapies correspond to antagonistic antibodies that block specific immune checkpoint molecules cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein (PD-1) and its ligand (PD-L1). The Food and Drug Administration (FDA) recently approved some of these drugs; in particular, we mention an anti-CTLA-4 antibody: Ipilimumab (trade name Yervoy®), approved in 2011 [2,3]; two anti-PD-1 monoclonal antibodies, Nivolumab (Opdivo®, in 2014 [4]) and Pembrolizumab (Keytruda®, in 2014 [5]); two anti-PD-L1 monoclonal antibodies, Avelumab (Bavencio®, in 2017 [6]) and Atezolizumab (Tecentriq®, in 2016 [7]).

The three types of immune checkpoints inhibitors (anti-CTLA-4, anti-PD-1 and anti-PD-L1) present the same mechanism of action: they block immune checkpoints, interfering with the normal functioning of the immune system. By unbalancing the immune system, they favor the development of a wide spectrum of autoimmune manifestations, also referred to as immune-related adverse events [8], some well-known [9] and others still to assess. The known adverse events include dermatologic, gastrointestinal, hepatic, endocrine, musculoskeletal, neurologic,

* Corresponding author at: Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Via Ferrata 5, 27100 Pavia, Italy.
E-mail address: elisamaria.zini01@universitadipavia.it (E.M. Zini).

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and other less common inflammatory events. They are usually caused by an excessive immune response, so they can be treated with corticosteroids, antihistamines or antitumor necrosis factor medications [10], which diminish the inflammation, but can also compromise the response to the therapy and may in turn introduce new adverse events. Accordingly, these medications should be administered only for the shortest period necessary to soothe the discomfort caused by the adverse event. The earlier an adverse event is detected, the shorter the treatment for that adverse event will be.

Since immunotherapy consists of an intravenous injection or infusion at the hospital, followed by two or three weeks at home, it is of utmost importance to continuously check the patients' status, in order to immediately acknowledge the onset of possible adverse events and trigger timely interventions when the patients are at home. This can be accomplished by asking the patient to report outcomes, which usually include symptoms and quality of life measures. These patient-reported outcomes (PROs) have been shown to improve symptom management, identification of psychosocial problems, and patient-provider communication [11].

In particular, electronic PROs (ePROs) [12], compared to the traditional paper-based measures, offer efficient standardized assessments, increased satisfaction, improved ease of use and increased quality of data [13]. Different scenarios for the collection of ePROs exist; the patients could be asked to self-report symptomatic adverse events at visits, using tablets or computers provided by the clinic [14]. However, given the importance of monitoring the patients also outside the hospital context, the best option is providing an application able to run on mobile devices, so that the patients can easily report, regardless of their location. Such a mobile application (app) should collect PROs, including both questionnaires on the quality of life and functionalities for adverse-event reporting, in addition to information about the patients' disease and actual treatments, provided by an authoritative source. The mobile app, provided to patients at the beginning of their treatment with the purpose of monitoring the disease evolution and the possible therapy side effects, should collect the reported adverse events in a structured form, to facilitate the analysis of the entered data and the integration with hospital databases. To accomplish this task, the use of standard terminologies is essential to help with representing the information to be acquired, as well as to favor its sharing and interpretation by electronic means.

To our knowledge, a standard set of PROs for the detection of immunotherapy-related adverse events is lacking. This could lead to ambiguity or even errors in the data collection and impair data reuse.

At the same time, a significant amount of information is contained in the patient information leaflets (PILs) of the drugs administered during immunotherapy, even though, unfortunately, all this information is in free text. Therefore, the aim of this study is to explore the standardization of the PILs contents and the subsequent development of an interface terminology based on the information extracted from the PILs. This interface terminology should be used in the future to facilitate the structured collection of adverse events using a mobile app. For this reason, and based on the User Interface Design Guidelines for Canada Health Infoway [15] prepared by Healthcare Human Factors [16], we argue that a searchable "flat" terminology could allow patients to find more easily the desired term. Some kind of support could be provided through an incremental searchable widget that allows the user to input free text and provides in real time the matching entries using auto-completion. Conversely, a hierarchical terminology can be confusing if the user is not familiar with the organizational structure of the data.

2. Materials and methods

In this section, we will describe the materials and tools we relied on for the standardization of the PILs and the subsequent development of the interface terminology about patient-reportable adverse events related to immunotherapy. To enable a better understanding of this process, Fig. 1 shows a diagram with the main steps, which will be described in the following subsections. Fig. 1 already contains also the outcome of the study that will be explained in the Results section.

2.1. Patient information leaflets analysis and symptoms extraction

The PILs represent a useful source of potential adverse events. We focused on the leaflets of the five immunotherapy drugs most recently approved by the FDA: Yervoy® (Ipilimumab), Opdivo® (Nivolumab), Keytruda® (Pembrolizumab), Tecentriq® (Atezolizumab) and Bavencio® (Avelumab). We considered both the English version,[1] revised by the European Medicines Agency (EMA), and its Italian translation[2] (not available for Tecentriq® and Bavencio®), edited by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), as we intend to use the interface terminology for Italian patients in our first pilot study.

According to the European regulation "EU Directive 2001/83/EC" [17], and its Italian transposition "DL 24 aprile 2006, n. 219" [18], all the leaflets present the same structure, following Annex III, Part B of the QRD (Quality Review of Documents) Human Product Information Template provided by the EMA [19]:

- Section 1: what the drug is and what it is used for.
- Section 2: what the patients need to know before they use the drug. This section presents a list of warnings and precautions, including the explanation and the most common symptoms of conditions that may be caused by the drug.
- Section 3: how to use the drug.
- Section 4: possible side effects. This section contains the list of possible side effects classified by frequency of occurrence, as reported by patients during clinical trials: very common (may affect more than 1 in 10 people), common (may affect up to 1 in 10 people), uncommon (may affect up to 1 in 100 people), rare (may affect up to 1 in 1000 people).
- Section 5: how to store the drug.
- Section 6: contents of the pack and other information.

Thus, the leaflets present an entire section (Section 4) dedicated to possible side effects. However, first of all, the information is presented in an unstructured form, as free text, and, secondly, some of these terms are better explained in other sections, which sometimes even precede the one containing the side effects. For example, in the Keytruda® leaflet, Section 4 reports "inflammation of the liver" as an uncommon adverse event, but its specific symptoms (e.g., "nausea", "vomiting", "dark urine", etc.) are listed in Section 2.

Therefore, as a first step, we manually extracted from Section 4 of the English version a list of adverse events. We avoided repetitions and we tried to separate the symptoms that can be directly reported by patients (e.g., nausea, pain, fever, urine color) from the conditions that can only be detected by physicians or through laboratory tests (e.g., hypo- or hyperthyroidism, inflammation of the liver or of the intestines). This was the phase of "PILs Analysis", with the subsequent generation of two sets, "Conditions" and "Symptoms", reported in Fig. 1. In a second step, we extracted from Section 2 the symptoms of the clinical conditions (phase of "Symptoms Explicitation", referring to the action of making the symptoms of the conditions explicit). We supplemented these symptoms with the list of patient-reportable adverse events, adding the missing symptoms and avoiding repeating those that were already present (phase of "Symptoms Deduplication").

Finally, we removed concepts that required clinical interpretation of basic physiological parameters (e.g., weight or blood pressure), as those

[1] The English PILs were retrieved from the site: https://www.medicines.org.uk/emc/ (last accessed October 2017).

[2] The Italian PILs were retrieved from the site: https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/ (last accessed October 2017).

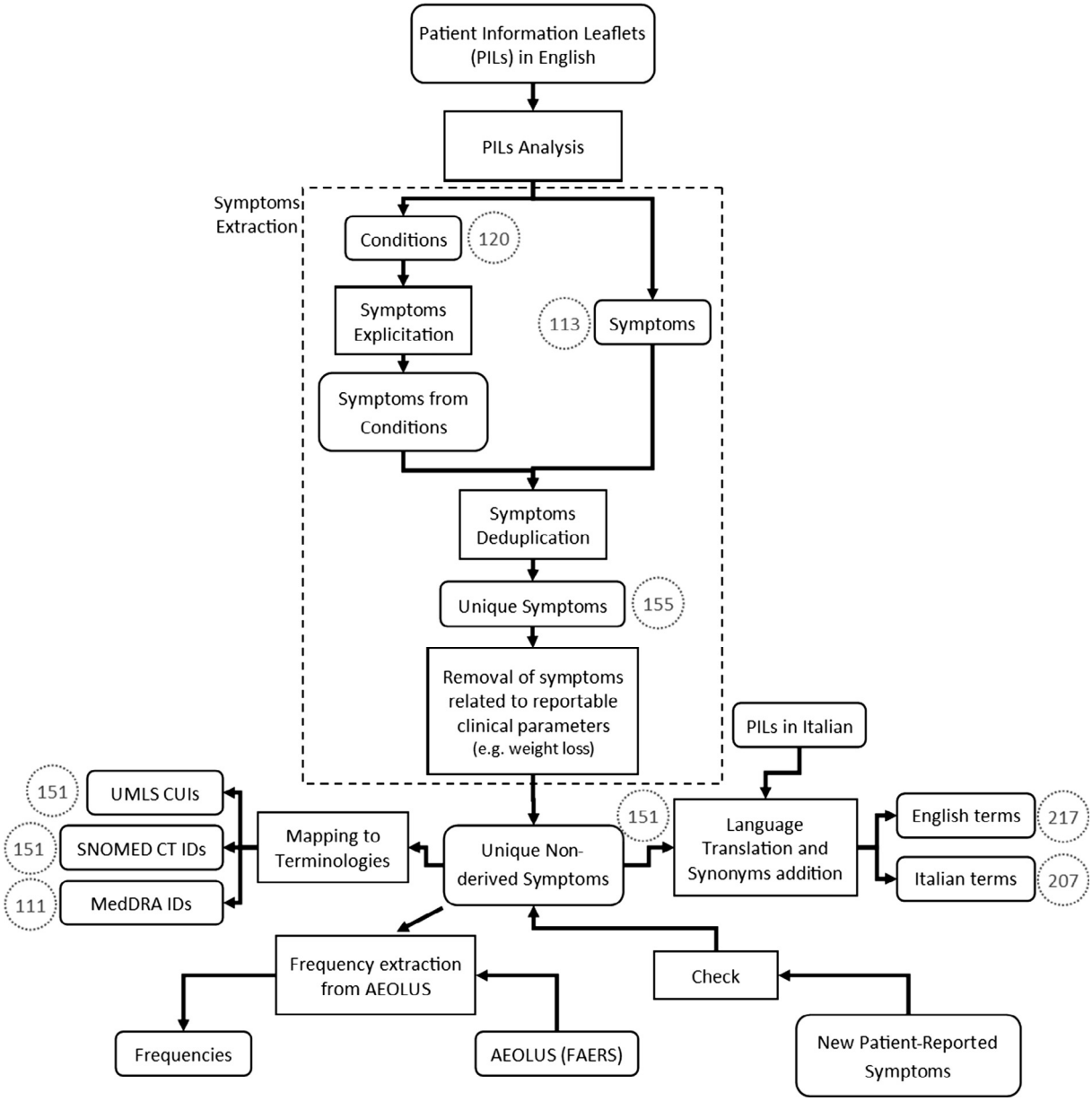

Fig. 1. Workflow for the standardization of the package information leaflets. The rectangles with round corners represent data, while the rectangles with straight corners represent processes. The dashed circles show the number of elements obtained in each step and will be explained in the Results section.

parameters are collected separately, leaving to PROs analysis tools the task to compute the increase or decrease of these quantities, based on the raw data sent.

2.2. Mapping to terminologies

2.2.1. Definition of interface terminology

Rosenbloom et al. define a clinical interface terminology as a systematic collection of health care related phrases (terms) that supports clinicians' entry of patient-related information into computer programs and decision support tools [20]. In general, interface terminologies are controlled vocabularies, which provide the translation from the natural language that professionals or patients use in their daily practice into more structured representations, processable by computers.

Bakhshi-Raiez et al. [21] propose a methodology to construct an interface terminology on SNOMED CT. The process includes six sequential phases: (1) domain analysis, (2) mapping from the domain concepts to SNOMED CT concepts, (3) creating the SNOMED CT subset guided by the mapping, (4) extending the subset with non-covered concepts, (5) constraining the subset by removing irrelevant content, and (6) deploying the subset in a terminology server.

Following this methodology, we exploited the concepts extracted from the PILs to develop an interface terminology, both in English and Italian, containing patient-reportable adverse events related to immunotherapy.

Domain analysis (phase 1) was already illustrated above, in the leaflet-related subsection; the following subsections will explain phases 2–5, while phase 6 is out of the scope of this paper and will be considered in the Discussion.

2.2.2. Mapping to reference terminologies

Once we had extracted the relevant concepts from the PILs, we mapped them to reference terminologies, in order to obtain a standardized vocabulary and facilitate the data reuse.

We considered different terminologies, starting from two collections of health-related vocabularies, the Observational Health Data Sciences and Informatics (OHDSI) Standard Vocabulary [22] and the Unified Medical Language System (UMLS) Metathesaurus [23]. Among the terminologies included by both OHDSI Standard Vocabulary and UMLS Metathesaurus, we can mention SNOMED CT and MedDRA (Medical Dictionary for Regulatory Activities), which we will discuss later in this section.

Both the OHDSI Standard Vocabulary and the UMLS Metathesaurus provide mapping structures among the vocabularies, allowing translations among them, but the UMLS Metathesaurus has the advantage of being concept-based. Conversely, the OHDSI Standard Vocabulary cannot be considered a concept-based terminology, because its identifiers change not only according to the concept, but also according to the specific vocabulary. For example, the concept of "Tachycardia" has a unique UMLS identifier (C0039231) linked to all the terminologies it includes. However, the same concept has different identifiers in OHDSI: 444070 is the identifier for SNOMED CT code "3424008 | Tachycardia", while 36311983 is the identifier for MedDRA code "10019303 | Heart rate increased". Moreover, UMLS also provides useful REST (REpresentational State Transfer) Application Programming Interfaces (APIs), which support web-based searches and content retrieval from the UMLS database.

As mentioned, SNOMED CT and MedDRA are two of the terminologies included by both the OHDSI Standard Vocabulary and the UMLS Metathesaurus. In particular, SNOMED CT is an international hierarchical and computer-processable collection of medical terms [24]. SNOMED CT can be used to represent and retrieve information from electronic health records (EHRs). It is considered one of the most suitable terminologies for comprehensively documenting clinical information [25]. On the other hand, MedDRA is a rich and standardized medical terminology, which aims to facilitate the sharing of regulatory information internationally for medical products used by humans. It is the adverse event classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [26].

In order to decide which reference terminology best fitted our aims, we thoroughly analyzed both terminologies and how they relate to the concepts in our domain, comparing the number of SNOMED CT and MedDRA identifiers that we could associate with our concepts. The Results section shows the results of this comparison.

As a first step, we manually mapped the list of concepts extracted from the PILs to SNOMED CT identifiers, using the SNOMED International SNOMED CT Browser [27]. We did not exploit the UMLS APIs for this task, because the results extracted through the APIs needed a further manual review. Moreover, the manual browsing of the SNOMED CT terminology allowed us to deduplicate terms that proved to be synonyms rather than different concepts. Then, we identified the UMLS Concept Unique Identifiers (CUIs) for those concepts and we exploited the UMLS APIs to automate the process of searching the related MedDRA codes.

The mapping operations were performed with the English version of the PILs because all the involved terminologies contained English terms, and availability of Italian terms was limited; therefore, the Italian terms were used only for the Italian translation of the interface terminology.

2.3. Extending the subset

In addition to the main definition of the concepts as extracted from the PILs, we added in the terminology all the synonyms that we found in the package leaflets, both in English and Italian, to provide a better match with the patients' expectations. These synonyms consist not only of different terms for the same concepts (e.g., "arthralgia" for "joints pain", or "tiredness" and "feeling tired" for "fatigue"), but also of alternative spelling variants (e.g., "diarrhea" for "diarrhoea") and derivative terms (e.g., "swollen ankles" for "swelling of ankle"). We did not consider the synonyms provided by the SNOMED CT Browser, because they are directed to health care professionals and therefore most of them are not commonly used by patients.

In order to avoid presenting patients with duplicates in the app interface, we used two distinct tags, "preferred terms" and "synonyms", to identify the two classes of terms, as in the common practice of many terminologies.

The concepts describing possible adverse events extracted from the PILs were highly detailed, since they included many events reported to the manufacturer during the clinical trials. Nonetheless, since immunotherapy is a recently introduced treatment, patients could experience and report side effects never reported before, as testified by the fact that all of these drugs are subject to additional monitoring by the EMA. Moreover, new immunotherapy drugs are frequently developed, tested and become available as soon as they are approved for use on patients. Therefore, we acknowledge that the terminology may be further extended, concerning both concepts and synonyms for already existing concepts. For this reason, we envisage a free text area in the app to allow patients to insert also the adverse events that they experience but that are not in the provided list. The insertion of a new concept or of a new synonymous term for a pre-existing concept should also be signaled for the interface terminology maintenance.

2.4. The adverse events reporting system

Another source of data we considered for our interface terminology was the FDA Adverse Event Reporting System (FAERS), a database containing information on adverse-event and medication-error reports submitted to FDA [28]. Since the FAERS data, although free and publicly available, present some imperfections such as duplicate records and lack of mapping to standard terminologies for drugs and adverse events, to take fully advantage of those, we exploited a dataset containing already processed FDA data. The resource, named Adverse Event Open Learning through Universal Standardization (AEOLUS), is freely available on the Dryad Digital Repository [29]. AEOLUS contains data from the FAERS, merging both legacy data, covering from January 2004 to August 2012, with current data, covering from September 2012 until today. The downloaded AEOLUS data cover from January 2004 until December 2014, but the authors of the AEOLUS data provide the code used to generate the dataset from the FDA raw data; the code is freely available on a public Github repository under the Apache License [30]. In fact, they did not simply merge these two sets of data, but they also processed the information, imputing missing values, removing duplicate records and mapping drugs and outcomes to OHDSI identifiers for RxNorm[3] and MeDRA Preferred Terms (PT) respectively. Finally, they generated a list of drug-outcome pairs from which they were able to calculate contingency tables, standardized reports and precomputed statistics for each drug-outcome pair. The included precomputed statistics are the Proportional Reporting Ratio (PRR) and the Reporting Odds Ratio (ROR) [32], which are measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. In particular, the PRR is the incidence of a particular adverse event reported by individuals taking a specific drug, compared to the incidence of the same adverse event reported by patients taking other drugs. AEOLUS also provides a mapping from OHDSI identifiers for MedDRA PT to OHDSI identifiers for SNOMED CT terms. They were able to map 80% of the reported adverse events to SNOMED CT.

In order to provide a baseline measurement of the number of concepts in our terminology that had already been reported to the FDA as

[3] RxNorm is a terminology that provides normalized names for clinical drugs and links those names to many of the drug vocabularies commonly used in pharmacy management and drug interaction software [31].

adverse events associated to the drugs we considered in the paper, we retrieved the statistics and contingency tables for those drugs and their outcomes. To this purpose, we exploited three tables of the AEOLUS database including drugs approved by 2014 (only three drugs among the five mentioned in the Introduction were referenced):

- The table "concept" contains all the types of concept. The *concept_ids* values are the OHDSI codes for the concepts, so the same concept can appear with different *concept_ids* according mainly to the domain, vocabulary, class, and validity.
- The table "standard_drug_outcome_statistics" contains the pre-computed statistics PRR and ROR for each drug-outcome pair, and their 95% confidence interval.
- The table "standard_drug_outcome_contingency_table" contains the contingency tables for each drug-outcome pair.

In the last two tables, the drugs are identified only through *concept_ids* related to the RxNorm vocabulary, while the outcomes are identified only through *concept_ids* related to the MedDRA vocabulary. Since we had a set of MedDRA identifiers for the outcomes, as explained above in the section regarding the mapping to reference terminologies, exploiting the table "concept" we could find the *concept_ids* for the desired outcomes. Moreover, searching by *concept_name*, we identified the *concept_ids* for the drugs. Through this information, we were able to extract the statistics and contingency tables for each desired drug-outcome pair from the tables "standard_drug_outcome_statistics" and "standard_drug_outcome_contingency_table".

Fig. 2 shows an example of the possible results obtainable through the search we described. In the example, we are looking for the statistics and contingency tables of the outcome "fatigue" for the drug Ipilimumab. For the sake of brevity, in the example we reported only the case of RxNorm code for Ipilimumab as "Ingredient". In Fig. 2, (a) is an extract of the table "concept", while (b) and (c) are extracts of the tables "standard_drug_outcome_statistics" and "standard_drug_outcome_contingency_table".

3. Results

3.1. Results of the standardization of the package information leaflets

We extracted 155 unique concepts from the PILs of Yervoy® (Ipilimumab), Opdivo® (Nivolumab), Keytruda® (Pembrolizumab), Tecentriq® (Atezolizumab) and Bavencio® (Avelumab). The whole set of concepts is shown in Appendix A. Appendix B shows the English and Italian synonyms for those concepts.

Table 1
Outline of the resulting list of Terms.

	English	Italian	Total
Preferred terms	151	151	302
Synonyms	66	56	122
Total	217	207	424

The already mentioned Fig. 1 shows in more detail the number of concepts found in each step of the process. The steps of "Symptoms Explicitation" from the conditions and "Symptoms Deduplication" were performed together. For example, consider the adverse event "inflammation of the liver", reported in Section 4 of the Keytruda® leaflet. Its symptoms are described in Section 2 of the leaflet. However, some of them, such as "vomiting" and "nausea", had already been referred as adverse events and thus were already present in the terminology. Others, such as "dark urine" or "yellowing of skin or white of eyes" (namely, jaundice) had to be added. Hence, the overall result is of 42 concepts added to the 113 patient-reportable symptoms. The total decreases to 151 as we remove the concepts "Weight gain", "Weight decreased", "Hypertensive disease" and "Hypotension", related to basic physiological parameters, as explained in the Methods subsection about PILs analysis. Finally, we identified 424 terms describing these concepts, considering both English and Italian and including synonyms in the count. This information is detailed in Table 1.

We were able to map all of the concepts to SNOMED CT, finding also the related UMLS CUIs and OHDSI codes. Since the adverse events described in the PILs were already highly detailed, we did not include also the hierarchically related terms, but we limited our subset to the terms found in the PILs.

On the contrary, we were not able to find the MedDRA codes for 13 concepts, while 33 other concepts only had a MedDRA Lowest Level Term (LLT) but no Preferred Term (PT). This results in 46 concepts without a MedDRA PT, so we could match 70% (105 out of 151) of our concepts to MedDRA. We could, however, associate 111 MedDRA codes with the remaining 105 concepts, because some UMLS CUIs were associated with more than one MedDRA code (e.g., UMLS "C0039231 | Tachycardia" is associated with MedDRA codes "10019303 | Heart rate increased" and "10043071 | Tachycardia").

These results show that SNOMED CT performed better than MedDRA; therefore, we chose to use SNOMED CT as the main coding system for our interface terminology.

(a) concept

concept_id	concept_name	domain_id	vocabulary_id	concept_class_id	standard_concept	concept_code	valid_start_date	valid_end_date	invalid_reason
35809076	fatigue	Condition	MedDRA	PT	C	10016256	1970-01-01	2099-12-31	
40238188	ipilimumab	Drug	RxNorm	Ingredient	S	1094833	2011-05-01	2099-12-31	

(b) standard_drug_outcome_statistics JOIN concept

drug_concept_id	drug_name	outcome_concept_id	outcome_name	prr	prr_95_percent_upper_confidence_limit	prr_95_percent_lower_confidence_limit	ror	ror_95_percent_upper_confidence_limit	ror_95_percent_lower_confidence_limit
40238188	ipilimumab	35809076	fatigue	2.06294	2.33887	1.81957	2.08466	2.36955	1.83402

(c) standard_drug_outcome_contingency_table JOIN concept

drug_concept_id	drug_name	outcome_concept_id	outcome_name	count_a	count_b	count_c	count_d
40238188	ipilimumab	35809076	fatigue	239	11699	588635	60066421

Fig. 2. Examples of concepts, statistics and contingency tables from the AEOLUS database. Statistics for the symptom "fatigue" and the drug "ipilimumab" are shown.

Table 2
Counts of the distinct outcomes in AEOLUS associated with the target drugs approved by 2014.

	Distinct outcomes	
Drugs	Present	Not present
Yervoy® (Ipilimumab)	90	21
Opdivo® (Nivolumab)	25	86
Keytruda® (Pembrolizumab)	45	66
Total	90	21

3.2. Results of statistics retrieval in AEOLUS

As we mentioned in the subsection concerning the FAERS, the AEOLUS database represents the adverse events only through OHDSI identifiers for MedDRA PTs. Hence, we were not able to retrieve contingency tables and statistics for the 46 concepts lacking a MedDRA PT. Considering the 111 outcome MedDRA codes we could retrieve, AEOLUS contained contingency tables and statistics for 90 outcomes associated with Ipilimumab, 25 associated with Nivolumab and 45 associated with Pembrolizumab, as shown in Table 2. Table 2 also shows that the outcomes associated with Nivolumab and Pembrolizumab in AEOLUS are a subset of the outcomes associated with Ipilimumab. These findings can be explained by the time of approval of the different drugs.

3.3. Preliminary validation

We performed a preliminary validation of the interface terminology considering a new immunotherapy drug: Imfinzi® (Durvalumab). This drug is very recent at the time of writing, to the point that no European documentation is available yet. For this reason, we considered its FDA label [33] and we can confirm that all the symptoms found in the label were already present in our terminology.

4. Discussion

In this study, we standardized the PILs, extracted all the mentioned adverse events and included them into an interface terminology specific for the collection of patient-reported adverse events concerning immunotherapy. We also mapped the terms to a reference terminology, in order to support and facilitate data reuse, and improve data quality.

As mentioned in the Introduction, the PILs contain well-controlled and accepted information about all the possible adverse events of a drug, including levels of probability derived from several research studies and clinical trials. However, the information is not provided in a structured form, but as free text, sometimes mentioning terms that may not be clear for people with low health literacy [34]. Moreover, the information about possible adverse events and their symptoms can be found in different sections of the leaflets. For this reason, our first attempt involved a manual effort of standardization of the PILs and generation of an interface terminology from the list of all the possible adverse events, linking it also to reference terminologies. This labor-intensive process is a limitation of the study, because it cannot be repeated easily for all the existing drugs of which we would like to list the possible adverse events. However, in order to have a baseline for starting the process automation, we needed to proceed with a manual effort at least once. In this way, we created a set of terms that could represent a gold standard for possible future Natural Language Processing algorithms for the automatic extraction of adverse events from the considered PILs and their mapping to reference terminologies.

The proposed interface terminology was designed to cover only the patient-reportable adverse events possibly caused by five immunotherapy drugs and reported in their PILs. These drugs, as stated in the Introduction, can be considered representative of immunotherapies that belong to the category of immune checkpoints inhibitors, since their mechanism of action is essentially the same.

The choice of not including all the adverse events reported through the FAERS derives from the knowledge that most of them concern conditions not reportable by patients (the FDA reporting system is usually used by health care professionals) and that some of them seem to be co-occurrent, but unrelated to the administration of the immunotherapy drugs (e.g., alcohol abuse or pregnancy). The decision to include only a relatively small set of concepts represents, therefore, a strength of this study, in terms of both orientation towards the patient as a primary user and maintainability of the system. In fact, the patients can query a small-size terminology more easily than the entire set of UMLS or SNOMED CT concepts. Other approaches to the construction of interface terminologies envisage the inclusion of a large number of terms, starting from a basic set of concepts and including all their children as found in a reference terminology [21,35,36]. This kind of interface terminologies could be suitable for health care professionals, but less for patients, who run the risk of being overwhelmed by the large amount of terms. Moreover, even in the case of health care professionals, a portion of these terms can be unused or not consistent with the context. Finally, the reduced size of the set of terms allows a faster and more feasible maintenance.

Nonetheless, we have the possibility of extending the terminology as needed, i.e., when the patients report an adverse event still unknown to the drugs manufacturers, or when they want to add a synonym for an already included adverse event.

In the sections Methods and Results, we highlighted that the choice of SNOMED CT as reference terminology for the concepts mapping was guided by its completeness in the context domain and its capability to map every concept extracted from the PILs; on the contrary, some of these concepts could not be found in MedDRA. We acknowledge that there is no perfect solution to the problem of finding a terminology able to map the vast majority of concepts, but we are confident that SNOMED CT is complete enough to cover all of the most common symptoms and findings. An issue to be solved for using SNOMED CT is that it requires licensing for use in clinical practice, Italy not being a member of SNOMED International. However, there are some fee exemptions applicable for SNOMED CT deployments in research projects in non-Member territories. On the other hand, MedDRA as well requires a license, providing fee exemptions for Non-Profit / Non-Commercial use.

4.1. Use of the interface terminology

Since the presented interface terminology includes more than 100 concepts and more than 150 terms per language to describe them, according to the User Interface Design Guidelines for Canada Health Infoway [15] prepared by Healthcare Human Factors [16], the best way to present them to the patients in an application is through a search bar. In fact, the presentation of the terms as a navigable hierarchical list could be less straightforward to the patients if they are not familiar with the organizational structure of the data. Nevertheless, the hierarchical structure is intrinsically provided by the mapping of the terms to SNOMED CT. Moreover, the hierarchical list assumes that the patients are also familiar with the preferred terms chosen by the developers of the terminology, while we would like to give patients a chance to search also using synonym terms, which inherently implies the use of free text.

Moreover, the search should be facilitated by the use of progressive matching and by ordering the concepts according to their incidence, showing as first the most frequently reported ones. We argue that a wider search could be implemented leveraging on the specific drug and patient's status. Furthermore, to maximize the information deriving from the collection of adverse events, they should also be better characterized and contextualized by attributes, such as severity, body site, number of occurrences of the event, and reporting of the ingestion of drugs aimed at soothing the discomfort.

About a possible technological solution for facilitating PROs collection, the interface terminology could be embedded into a mobile app, and we could envisage a remote updating of the interface terminology, deploying it on a remote server that the app would query to update its local database. In this way, even if the device lacks internet connection, the app would still query the terminology to show the results of the search to the user, with the only downside of having a potentially older version of the terminology. We envisage developing a generic application for collecting ePROs that is configurable and extendable, adding the terminology as a plug-in. In this way, for a new therapy to monitor, we could just add another interface terminology in the app. In this perspective, we believe that a separation of the development of the interface terminology itself from the description of the app functionalities was necessary. The app will be a future development, not necessarily bound to the terminologies it will contain.

A future study will allow evaluating the completeness of the terminology, in terms of both concepts and synonyms. Moreover, the study will assess the effectiveness of the interface terminology in supporting the recording of reported adverse events and in improving the quality of collected data, since the use of this terminology will allow obtaining data that are structured and easy to reuse.

The app, besides the basic function of reporting the events to the doctors for monitoring purposes, could also be used in clinical trials aimed at comparing the incidence of the adverse events reported by specific groups of patients to the incidence of the adverse events mentioned in the PILs of the considered drugs. It is also relevant to compare the reported incidence to the incidence of adverse events for the drugs computed from the reports to the FDA.

The pre-computed PRR provided by the AEOLUS database can also be used to find all the other possible causes of the reported adverse events and use this information in a decision support system for the clinicians. In fact, an adverse event could have other causes than immunotherapy. To give an example, if the patient has a rash, the most probable cause is the immunotherapy treatment, but it could also be another drug administered in the same period.

One of the main limitations in the use of AEOLUS consists in the fact that it contains only data until December 2014. As shown in Table 2, this results in very few contingency tables for the drugs approved in 2014 (Opdivo® and Keytruda®). Nonetheless, we can overcome this limitation by adjusting and running the code that AEOLUS creators provide to recreate the dataset from the FDA raw data.

A valuable alternative to AEOLUS is represented by the Linked Data of the project Data2Semantics [37]. They created a Linked Data version of FAERS, linking every name to its normalized form, linking drugs to UMLS, Drugbank, DBPedia, and Sider and linking diagnoses to UMLS, LinkedCT, CTCAE, and Sider. The result is a Linked Data browser called AERS-LD (AERS-Linked Data) [38]. As AERS-LD includes FDA data until 2012 only, we will consider the addition of the most recent FDA data and the use of AERS-LD data in the future.

5. Conclusion

PILs provide a valuable source for determining adverse events, but they mix patient-reportable and clinically assessable events. In this paper we described the standardization of PILs through the extraction of the adverse events mentioned and their inclusion in an interface terminology specifically designed for the collection of patient-reported adverse events concerning immunotherapy. The resulting interface terminology includes Italian and English terms for 151 patient-reportable adverse events. The concepts were also mapped to reference terminologies, in order to support and facilitate data reuse and to improve data quality.

A preliminary validation on the FDA label of a new immunotherapy drug showed that our interface terminology already contained all the mentioned symptoms.

Further work will be undertaken to evaluate the usability of the interface terminology and the patients' experience and satisfaction with the proposed terms, as well as its effectiveness on data quality and quality of care [39–41].

Conflict of interest

The authors declared that there is no conflict of interest.

Appendix A. List of the extracted concepts with their English and Italian preferred terms

#	English Preferred Term	Italian Preferred Term	UMLS CUI	UMLS Concept Name
1	Abdominal pain	Dolore addominale	C0000737	Abdominal pain
2	Absence of menstrual periods	Assenza di cicli mestruali	C0002453	Amenorrhea
3	Allergic reaction (related to the infusion of the medicine)	Reazione allergica (dovuta all'infusione del medicinale)	C0013182	Drug allergy
4	Back pain	Dolore alla schiena	C0004604	Back pain
5	Bleeding in the eye	Emorragia oculare	C0015402	Eye hemorrhage
6	Blisters	Vesciche	C0005758	Bulla
7	Blisters on feet	Vesciche sui piedi	C2919517	Blister of foot
8	Blisters on hands	Vesciche sulle mani	C0587295	Traumatic blister of hand
9	Blood clots	Coaguli di sangue	C0302148	Blood clot
10	Blood in urine	Sangue nelle urine	C0018965	Hematuria
11	Bloody stools	Sangue nelle feci	C0018932	Hematochezia
12	Blurred vision	Visione offuscata	C0344232	Blurred vision
13	Brief involuntary muscle contraction	Breve contrazione involontaria dei muscoli	C0235086	Involuntary muscle contraction
14	Burning pain of the arms and legs	Dolore bruciante a gambe o braccia	C0030196	Pain in limb
15	Burning sensation while urinating	Sensazione di bruciore durante la minzione	C0423736	Scalding pain on urination
16	Change in voice (gets deeper)	Cambiamento della voce (più profonda)	C0518179	Change in voice
17	Change in your sense of taste	Cambiamento nel senso del gusto	C0013378	Dysgeusia
18	Changes in behavior	Cambiamenti nel comportamento	C0542299	Behavioral change
19	Chest pain	Dolore al petto	C0008031	Chest pain
20	Chest tightness	Sensazione di oppressione al torace	C0232292	Chest tightness
21	Chills	Brividi	C0085593	Chills

22	Cloudy urine	Urina torbida	C0278034	Cloudy urine
23	Cold sores	Vescicole labiali	C0038362	Stomatitis
24	Confusion	Confusione	C0009676	Confusion
25	Constipation	Stipsi	C0009806	Constipation
26	Cough	Tosse	C0010200	Coughing
27	Cramps	Crampi	C0026821	Muscle cramp
28	Dark stool	Feci scure	C0474585	Feces color: tarry
29	Dark urine	Urina scura	C0426396	Urine looks dark
30	Decreased appetite	Diminuzione dell'appetito	C0232462	Decrease in appetite
31	Decreased hearing	Diminuzione dell'udito	C1384666	Hearing impairment
32	Decreased volume of urine	Ridotta quantità di urine	C0028961	Oliguria
33	Depression	Depressione	C0011581	Depressive disorder
34	Diarrhoea (watery, loose or soft stool)	Diarrea (feci acquose, liquide, molli o soffici)	C0011991	Diarrhea
35	Difficulty breathing	Difficoltà di respirazione	C0013404	Dyspnea
36	Difficulty in coordinating movements	Difficoltà di coordinazione dei movimenti	C0004134	Ataxia
37	Difficulty in speaking	Difficoltà nel parlare	C1527347	Difficulty speaking
38	Difficulty in urinating	Difficoltà a urinare	C0013428	Dysuria
39	Difficulty swallowing	Difficoltà a deglutire	C0011168	Deglutition disorders
40	Difficulty walking	Difficoltà a camminare	C0311394	Difficulty walking
41	Dizziness	Capogiri	C0012833	Dizziness
42	Double vision	Vedere doppio	C0012569	Diplopia
43	Drooping eyelid	Palpebra calante	C0005745	Blepharoptosis
44	Drowsiness	Sonnolenza	C0013144	Drowsiness
45	Dry eyes	Secchezza dell'occhio	C0314719	Dryness of eye
46	Dry mouth	Bocca secca	C0043352	Xerostomia
47	Dry skin	Pelle secca	C0151908	Dry skin
48	Easy bleeding	Facilità di sanguinamento	C0424560	Bleeds easily
49	Easy bruising	Facile formazione di lividi	C0423798	Increased tendency to bruise
50	Enlargement of a lymph node	Ingrossamento di un linfonodo	C0497156	Lymphadenopathy
51	Excessive sweating at night	Sudorazione notturna eccessiva	C0028081	Night sweats
52	Excessive thirst	Sete eccessiva	C0085602	Polydipsia
53	Eye muscle inflammation	Infiammazione del muscolo degli occhi	C2350476	Orbital myositis
54	Eye or skin yellowing (jaundice)	Colorazione gialla degli occhi o della pelle (ittero)	C0022346	Icterus
55	Face swelling	Gonfiore del viso	C0151602	Facial swelling
56	Fainting	Svenimento	C0039070	Syncope
57	Fatigue	Stanchezza	C0015672	Fatigue
58	Feeling cold	Sensazione di freddo	C0812387	Feels cold
59	Feeling of intense heat	Sensazione di caldo intenso	C2939147	Feels hot
60	Fever	Febbre	C0015967	Fever
61	Flu-like illness	Malattia simil influenzale	C0521839	Influenza-like illness
62	Foot drop	Piede cadente	C0085684	Foot-drop
63	Foreign body sensation in the eyes	Sensazione di corpo estraneo negli occhi	C0234658	Feeling of sand or foreign body in eye
64	Forgetfulness	Tendenza a dimenticare	C0233794	Memory impairment
65	Frequent need to urinate	Necessità di urinare spesso	C0085606	Urgency of micturition
66	Frequent urge to defecate	Stimolo urgente alla defecazione	C0426636	Urgent desire for stool
67	Hair colour changes	Cambiamenti del colore dei capelli	C0474378	Hair color change
68	Headache	Mal di testa	C0018681	Headache
69	Heartburn	Sensazione di bruciore allo stomaco	C0018834	Heartburn
70	High blood pressure	Pressione arteriosa alta	C0020538	Hypertensive disease
71	Increased amount of urine	Quantità di urina notevolmente aumentata	C0032617	Polyuria
72	Increased appetite	Aumento di appetito	C0232461	Increased appetite
73	Inflammation of the anus	Infiammazione dell'ano	C0238634	Anal inflammation
74	Inflammation of the coloured part of the eye	Infiammazione della parte colorata dell'occhio	C0022081	Iritis
75	Inflammation of the eye	Infiammazione degli occhi	C0014236	Endophthalmitis
76	Inflammation of the eyelids	Infiammazione delle palpebre	C0005741	Blepharitis
77	Inflammation of the food pipe	Infiammazione dell'esofago	C0014868	Esophagitis
78	Inflammation of the joints	Infiammazione delle articolazioni	C0003864	Arthritis
79	Inflammation of the rectal wall	Infiammazione della parete del retto	C0033246	Proctitis
80	Inflammation of the skin	Infiammazione della cute	C0011603	Dermatitis
81	Irritable mood	Irritabilità	C0022107	Irritable mood
82	Itchiness of the eyes	Prurito degli occhi	C0022281	Itching of eye
83	Itching	Prurito	C0033774	Pruritus
84	Itchy hives	Eruzione pruriginosa	C0042109	Urticaria
85	Joints pain	Dolore alle articolazioni	C0003862	Arthralgia
86	Low blood pressure	Pressione arteriosa bassa	C0020649	Hypotension

87	Low blood pressure when standing up	Capogiri nell'alzarsi in piedi	C0234987	Postural dizziness
88	Lowered sex drive	Ridotto stimolo sessuale	C0020594	Hypoactive sexual desire disorder
89	Lumps	Noduli	C0577559	Mass of body structure
90	Mood swings	Cambiamenti di umore	C0085633	Mood swings
91	Mouth ulcers	Ulcere della bocca	C0149745	Oral ulcer
92	Mucus in stool	Muco nelle feci	C0241254	Mucus in stool
93	Muscle pain	Dolori muscolari	C0231528	Myalgia
94	Muscle spasm	Spasmo muscolare	C0037763	Spasm
95	Muscle tenderness	Indolenzimento muscolare	C0575064	Skeletal muscle tender
96	Muscle weakness	Debolezza muscolare	C0151786	Muscle weakness
97	Musculoskeletal pain	Dolore muscolo-scheletrico	C0026858	Musculoskeletal pain
98	Nasal congestion	Congestione nasale	C0027424	Nasal congestion
99	Nausea	Nausea	C0027497	Nausea
100	Neck stiffness	Rigidità del collo	C0151315	Neck stiffness
101	Numb fingers	Intorpidimento delle dita delle mani	C0587054	Numbness of finger
102	Numb toes	Intorpidimento delle dita dei piedi	C0587056	Numbness of toe
103	Numbness	Intorpidimento	C0028643	Numbness
104	Oedema	Edema	C0013604	Edema
105	Pain	Dolore	C0030193	Pain
106	Pain in the bones	Dolore alle ossa	C0151825	Bone pain
107	Pain in the eye	Dolore agli occhi	C0151827	Eye pain
108	Pain on the right side of the stomach area	Dolore nella parte destra dell'addome	C0522067	Liver pain
109	Painful skin lesion of the arms and legs and face	Lesioni cutanee dolorose delle braccia e delle gambe e del viso	C0014743	Erythema nodosum
110	Pale stool	Feci pallide	C0232720	Pale feces
111	Paralysis in the extremities	Paralisi delle estremità	C0522224	Paralysed
112	Rapid heart rate	Battito cardiaco veloce	C0039231	Tachycardia
113	Reaction at site of injection	Reazioni nel sito di iniezione	C0151735	Injection site reaction
114	Red eye	Rossore degli occhi	C0235267	Redness of eye
115	Red itchy spots (similar to measles)	Macchie rosse pruriginose (simili a morbillo)	C0014742	Erythema multiforme
116	Redness of the skin	Arrossamento della pelle	C0041834	Erythema
117	Reduced vision	Riduzione della vista	C0558171	Deteriorating vision
118	Runny eyes	Occhi lacrimanti	C3257803	Watery eyes
119	Runny nose	Naso che cola	C1260880	Rhinorrhea
120	Seeing spots	Vedere macchie	C1690946	Seeing spots in front of eyes
121	Seizure	Convulsioni	C0036572	Seizures
122	Severe peeling of the skin	Desquamazione grave della pelle	C0237849	Peeling of skin
123	Skin bumps	Tumefazioni	C0281982	Swelling of skin
124	Skin rash	Eruzione cutanea	C0015230	Exanthema
125	Sneezing	Starnuti	C0037383	Sneezing
126	Sores	Piaghe	C3241942	Sore on skin
127	Stiffness	Rigidità	C0427008	Stiffness
128	Stiffness in the hip	Rigidità dell'anca	C0239957	Hip stiff
129	Stiffness in the shoulder	Rigidità della spalla	C0241042	Shoulder stiff
130	Stomach pain	Dolore di stomaco	C0221512	Stomach ache
131	Sweating	Aumento della sudorazione	C0700590	Increased sweating
132	Swelling	Gonfiore	C0038999	Swelling
133	Swelling of ankle	Gonfiore delle caviglie	C0235439	Ankle edema
134	Swelling of arm	Gonfiore delle braccia	C0577598	Swelling of arm
135	Swelling of feet	Gonfiore dei piedi	C0574002	Edema of foot
136	Swelling of hands	Gonfiore delle mani	C0575805	Swelling of hands
137	Swelling of leg	Gonfiore delle gambe	C0581394	Swollen legs
138	Swelling of the eye	Gonfiore degli occhi	C0270996	Swelling of structure of eye
139	Swelling of the thyroid gland	Gonfiore della tiroide	C0018021	Goiter
140	Temporary redness of the face and neck	Arrossamento temporaneo del viso e del collo	C0016382	Flushing
141	Tender red bumps under the skin	Tumefazioni rosse e dolenti sotto cute	C0151811	Subcutaneous nodule
142	Thickened patches of red skin with silvery scales (psoriasis)	Chiazze ispessite di pelle arrossata con scaglie argentee (psoriasi)	C0033860	Psoriasis
143	Tingling of the arms or legs or feet	Formicolio a gambe o braccia	C0423572	Pins and needles
144	Toes and fingers pale	Pallore delle dita dei piedi e delle mani	C0678215	Patient observed to be pale
145	Trouble sleeping	Disturbi del sonno	C0235162	Difficulty sleeping
146	Tumour pain	Dolore nella sede del tumore	C1719395	Pain due to neoplastic disease
147	Uncomfortable sensitivity to light	Sensibilità fastidiosa alla luce	C0085636	Photophobia
148	Unusual hair loss	Perdita di capelli inusuale	C0002170	Alopecia

149	Unusually red nose and cheeks (rosacea)	Naso e guance insolitamente rosse (rosacea)	C0035854	Rosacea
150	Vitiligo	Vitiligine	C0042900	Vitiligo
151	Vomiting	Vomito	C0042963	Vomiting
152	Weakness	Debolezza	C0004093	Asthenia
153	Weight gain	Aumento di peso	C0043094	Weight gain
154	Weight loss	Perdita di peso	C1262477	Weight decreased
155	Wheezing	Rantolo	C0043144	Wheezing

Appendix B. List of the English and Italian synonyms for the concepts listed in Appendix A

English Synonyms

UMLS CUI	Synonym
C0000737	Abdominal tenderness
C0002170	Hair thinning
C0003862	Arthralgia
C0003864	Arthritis
C0004093	Feeling weak
C0004093	Lack of energy
C0011991	Diarrhea (watery, loose or soft stool)
C0013144	Sleepiness
C0013144	Somnolence
C0013144	Feeling drowsy
C0013144	Feeling sleepy
C0013404	Shortness of breath
C0013428	Pain while urinating
C0015672	Tiredness
C0015672	Feeling tired
C0016382	Flushing
C0022081	Inflammation of the iris
C0022107	Irritability
C0027424	Blocked nose
C0027497	Feeling sick
C0027497	Sickness
C0035854	Acne-like skin problem
C0036572	Convulsion
C0038362	Stomatitis
C0039231	Fast heart beat
C0039231	Rapid heart beat
C0039231	Fast heart rate
C0085606	Need to urinate more often
C0042109	Itchy rash
C0042109	Wheal
C0042109	Bumpy rash
C0042109	Weal
C0042900	Skin colour change in patches
C0085593	Shivering
C0085593	Shaking
C0085633	Changes in mood
C0085636	Intolerance of bright light
C0149745	Mouth sores
C0151602	Facial swelling
C0221512	Stomach ache
C0221512	Belly pain
C0231528	Pain in the muscles
C0231528	Aching muscles
C0232292	Feeling pressure in chest
C0232461	Feeling more hungry than usual
C0232462	Feeling less hungry than usual
C0232462	Loss of appetite
C0233794	Memory problems
C0234987	Dizziness when standing up
C0235267	Redness of the eye
C0235439	Swollen ankles

C0270996	Swollen eyes
C0474585	Tarry stool
C0474585	Black stool
C0474585	Sticky stool
C0542299	Altered behaviour
C0542299	Changes in behaviour
C0542299	Altered behavior
C0542299	Behavioral change
C0574002	Swollen feet
C0575805	Swollen hands
C0577598	Swollen arms
C0581394	Swollen legs
C1260880	Rhinorrhea
C1260880	Rhinorrhoea
C2939147	Hot flush

Italian Synonyms

UMLS CUI	Synonym
C0002170	Assottigliamento dei capelli
C0003862	Artralgia
C0003864	Artrite
C0004093	Mancanza di energie
C0004093	Sentirsi debole
C0012569	Visione doppia
C0012833	Stordimento
C0012833	Vertigini
C0013144	Sentirsi assonnati
C0013404	Respiro corto
C0013428	Dolore nell'urinare
C0015230	Sfogo cutaneo
C0015230	Rash cutaneo
C0015402	Sanguinamento dell'occhio
C0015672	Affaticamento
C0015672	Sentirsi stanchi
C0022081	Infiammazione dell'iride
C0027424	Naso bloccato
C0027424	Naso tappato
C0027497	Sensazione di malessere
C0035854	Problema cutaneo simile all'acne
C0038362	Stomatite
C0041834	Eritema
C0085606	Bisogno di urinare spesso
C0085606	Minzione frequente
C0085606	Urgenza di urinare spesso
C0042109	Orticaria pruriginosa
C0042109	Eruzione urticante
C0042900	Alterazione del colore della pelle con chiazze
C0043144	Respiro ansimante
C0085636	Intolleranza alla luce intensa
C0149745	Vesciche in bocca
C0151602	Gonfiore della faccia
C0151602	Faccia gonfia
C0221512	Mal di stomaco
C0232292	Sensazione di oppressione al petto
C0232461	Sentirsi più affamati del solito
C0232462	Perdita di appetito
C0233794	Problemi di memoria
C0234987	Pressione arteriosa bassa al momento di alzarsi
C0235162	Difficoltà a dormire
C0235267	Arrossamento degli occhi
C0235267	Occhi rossi

C0235439	Caviglie gonfie
C0270996	Occhi gonfi
C0314719	Secchezza oculare
C0314719	Occhio secco
C0423736	Sensazione di bruciore nell'urinare
C0474585	Feci nere o nerastre
C0542299	Comportamento diverso dal solito
C0542299	Comportamento alterato
C0577559	Protuberanze
C0577598	Braccia gonfie
C0581394	Gambe gonfie
C1260880	Rinorrea
C2939147	Vampate

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